IN THE UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF VIRGINIA
Alexandria Division

HALOZYME, INC. Plaintiff, v. JOSEPH MATAL, performing the functions and duties of Under Secretary of Commerce for Intellectual Property and Director of the United States Patent and Trademark Office, Defendant.	Case 1:16-cv-01580-CMH-JFA

HALOZYME'S BRIEF IN SUPPORT OF ITS MOTION FOR PARTIAL SUMMARY JUDGMENT AND IN OPPOSITION TO THE U.S. PATENT AND TRADEMARK OFFICE'S MOTION FOR SUMMARY JUDGMENT

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INTRODUCTION

The PTO's motion for summary judgment proceeds from a flawed premise: That the facts material to the patentability of Claims 295 through 298, 300, and 303 of U.S. Patent Application Serial No. 11/238,171 ("the '171 Application" and the "Pending Claims") are not in dispute and, therefore, the Court can effectively rule on the administrative record that was before the Patent Trial and Appeal Board ("PTAB") as a matter of law. But 35 U.S.C. § 145 affords Halozyme the right to bring evidence not before the PTAB, and not in the Administrative Record. The Supreme Court makes clear that if a plaintiff does that, then the district court must engage in *de novo* fact finding with no deference to the Administrative Record.

Halozyme has taken full advantage of its statutory right to correct, with evidence from leading experts, what is a fundamentally-erroneous PTAB decision on obviousness type double-patenting ("ODP"). That determination, while ultimately a matter of law, rests on underlying factual issues, namely the four Supreme Court *Graham* obviousness factors. Underlying factual disputes are resolved at trial, not by way of summary judgment.

The PTO argues that somehow Halozyme is "unjustifiably" trying to extend patent protection through its Pending Claims in view of three other issued Halozyme patents. But that argument has no merit on at least three grounds. First, it is well-settled that patentably distinct claims, as here, invoke no ODP concerns. Second, the patents and the pending patent application all come from the same patent family. As a result, there would have been no extended patent protection on the Pending Claims if granted in the first place. And the statutory term adjustment if the PTO's decision is reversed may not be fairly characterized as "unjustifiable." Finally, the PTO never contended (before the PTAB or this Court) that those three patents alone render Halozyme's Pending Claims obvious, *i.e.*, patentably indistinct.

Instead, the Examiner resorted to additional references, and rejected the Pending Claims

"in view of Braxton and Thompson." Thus, the at-issue rejections rest on a combination of references – the issued patent claims and Braxton and Thompson references – introducing a number of underlying factual inquiries. Those inquiries include whether the references fairly suggest the missing claim element and, whether a skilled artisan would be motivated to combine the references and have a reasonable expectation of success.

Halozyme stands ready to present substantial evidence on these and other issues. Halozyme has generated over 300 pages of expert reports supported by extensive art on this issue. Specifically, Drs. Samuel Zalipsky and Bruno Flamion will testify that the PTAB erred and that the '171 Application's Pending Claims (a) are not obvious variants of claims 9 and 10 of U.S. Patent No. 7,767,429 in view of U.S. Patent Nos. 5,766,897 ("Braxton") and 6,552,170 ("Thompson"), (b) are not obvious variants of claims 4 and 5 of U.S. Patent No. 7,846,431 in view of Braxton and Thompson, and (c) are not obvious variants of claims 5 and 6 of U.S. Patent No. 7,829,081 in view of Braxton and Thompson. That alone is enough to defeat the PTO's motion for summary judgment. *Edwards Systems Technology, Inc. v. Digital Control Systems, Inc.*, 99 Fed. Appx. 911, 921 (Fed. Cir. 2004) ("battle of the experts" render summary judgment improper); *LifeNet Health v. LifeCell Corp.*, No. 2:13CV486, 2014 WL 5456521, at *12 (E.D. Va. Oct. 27, 2014) (*citing Crown Packaging Tech., Inc. v. Ball Metal Beverage Container Corp.*, 635 F.3d 1373, 1384 (Fed. Cir. 2011). The PTO's motion does not account for this extensive evidence that the PTAB never considered.

But more importantly, that evidence does not just create an "issue of fact." It shows the PTAB's manifest error in relying on the Braxton and Thompson references. Simply put, those references teach a technique that would likely *destroy* the activity of the claimed pharmaceutical composition that is formulated for systemic (whole body) application comprising a specific

human-derived hyaluronidase with about three to six PEG-moieties – a fact the PTAB or Examiner *never* addressed.

Faced with this, the PTO (1) points to language either in the background of those two references that in fact teaches away and criticizes the very alleged routine experimentation the PTO advances or (2) quotes snippets out of context. That approach errs, because what a reference teaches and does not teach must be based on the whole reference and is a factual issue.

The need for a trial on the secondary considerations of nonobviousness is equally stark. Halozyme has evidence that third parties – investors and collaborators – have made economic decisions to support Halozyme and the PEGPH20 product that the '171 Application covers. Investors have pumped millions of dollars into Halozyme for the development of PEGPH20, and scientists and medical institutions have entered agreements with Halozyme to further research PEGPH20. Drs. Zalipsky and Flamion will also testify that the '171 Application represents unexpected results, satisfies a long-felt but unmet need in the treatment of pancreatic cancer, and has received industry praise and recognition. These factual disputes further warrant denial.

Pressed by this factual record, the PTO resorts to highly flawed arguments that lack basis in the plain claim language or in the law. For example, the PTO claims that the term "pharmaceutical composition" is not limiting because it is in the Pending Claims' preamble. But that same term is in the body of the claims, and thus, as a matter of law, is limiting. The PTO's other arguments, as discussed below, likewise do not withstand scrutiny.

The PTO's motion in essence asks the Court to presume that it got this decision right and that this Court should accept its characterization of the facts. We know (1) from PTAB patent denials reversed by federal courts and (2) from PTO patent grants invalidated by federal courts, that through the judicial process, PTO errors are rectified. The facts here will show at trial that

the PTAB's decision errs and should be judicially rectified.

Finally, Halozyme cross moves for partial summary judgment of the PTAB's decision that the '171 Application is rendered obvious under 35 U.S.C. § 103 by WO 2004/078140 ("Bookbinder") in view of Braxton and Thompson. It is undisputed that the priority date for the Pending Claims is the earlier-filed U.S. Patent Application Serial No. 11/065,716 ("the '716 Application"), dated February 23, 2005. The '716 Application contains sufficient written description and enablement to entitle the '171 Application's Pending Claims to the earlier priority date of the '716 Application and the PTO has not contended otherwise in Interrogatory responses. The inventors are the same on the '171 Application and Bookbinder. Therefore, as discussed herein, the Bookbinder reference relied on as the primary reference for the obviousness rejection legally does not satisfy the requirements of prior art under 35 U.S.C. § 102 and therefore legally cannot serve as a reference for an obviousness rejection under Section 103.

Accordingly, Halozyme requests that the PTO's motion for summary judgment be denied, and Halozyme's cross motion for partial summary judgment be granted.

STATEMENT OF UNDISPUTED MATERIAL FACTS SUPPORTING HALOZYME'S MOTION FOR PARTIAL SUMMARY JUDGMENT

1. U.S. Patent Application Serial No. 11/065,716 (the '716 Application) was filed on February 23, 2005. (Ex. A, Kim Decl., Ex. 2.) The '171 Application is a continuation-in-part of, and claims priority to, the '716 Application, as the Administrative Record reflects. (A1182.)

2. The '716 Application provides at least two paragraphs of written description of generating "rHuPH20s reproducibly comprising a combination of molecules having between about three to six PEG molecules per sHASEGP." (Ex. A, Ex. 2, '716 Application, ¶¶ 815-16.) Paragraph 816 of the '716 Application discloses that these pharmaceutical compositions were intravenously administered (systemic administration) in mice, and showed a 16-20 fold increase

in serum half-life over unmodified sHASEGP and further provided therapeutic benefit in a rat stroke model. (*Id.*) Further analysis of the written description and enablement support in the '716 Application for the Pending Claims is set forth at Zalipsky Rebuttal Rep. ¶¶ 53-54 and incorporated herein. (Ex. A, Ex. 86, Zalipsky Rebuttal Rep. ¶¶ 53-54.)

3. The '716 Application adequately describes and enables the Pending Claims of the '171 Application. (Ex. A, Ex. 1, Corr. Zalipsky Rep. ¶¶ 70–71.)

4. The PTO in Interrogatory Responses did not assert that the Pending Claims lack written description and enablement support in the '716 Application when asked to identify if the Pending Claims are not entitled to the "claimed priority date of February 23, 2005." (Ex. A, Ex. 107, Def. Third Supp Response to 1st Set of Interrogs, pp. 5-6.)

5. On October 16, 2007, during the prosecution of the '171 Application, the PTO issued a restriction requirement. (A442-452.)

6. In response, and after electing the Pending Claims to be pursued for prosecution, Petitions to Correct Inventorship were filed on April 16, 2008 and on October 7, 2010. (A453-454, A721-727.) Those petitions identified Louis Bookbinder, Anirban Kundu and Gregory Frost as the joint inventors on the '171 Application. (*Id.*)

7. The PTO formally corrected inventorship on the '171 Application identifying Louis Bookbinder, Anirban Kundu and Gregory Frost as the joint inventors. (A1182.)

8. WO 2004/078140 (Bookbinder) published on September 16, 2004, and lists Louis Bookbinder, Anirban Kundu and Gregory Frost as the joint inventors. (A1332.) Therefore, Bookbinder published less than one year prior to the '171 Application's claimed priority date of the '716 Application, which was filed on February 23, 2005. (*See* SUMF No. 1 *supra*.)

9. The inventors on Bookbinder and the '171 Application are the same. (*See* SUMF

Nos. 7 and 8 *supra*.)

10. The Examiner rejected, and the PTAB affirmed, the Pending Claims under 35 U.S.C. § 103 as unpatentable over Bookbinder, Braxton, and Thompson. (A2210-19.)

HALOZYME'S RESPONSE TO THE PTO'S "STATEMENT OF UNDISPUTED MATERIAL FACTS" ("SUMF")

The disputed facts described below remain as material facts as to which there exist genuine issues necessary to be litigated at trial.

1. PTO's SUMF ¶ 1. Undisputed.

2. PTO's SUMF ¶ 2. Disputed to the extent this statement is taken out of context or purports to set forth all of the disclosures made in the '171 Application. The patent application speaks for itself and the specific claims at issue are directed to a pharmaceutical composition formulated for systemic administration comprising specific forms of human-derived hyaluronidase modified with about 3 to 6 PEG moieties. (*See* SUF, ECF No. 76, ¶ 7.)

3. PTO's SUMF ¶ 3. Disputed to the extent this statement is taken out of context or purports to set forth all of the disclosures made in the '171 Application. Disputed on relevance in that for obviousness type double patenting, reference to the specification is limited primarily to claim construction and this alleged fact is not being proffered for that purpose. *See Eli Lilly & Co. v. Teva Parenteral Meds., Inc.*, 689 F.3d 1368, 1380 (Fed. Cir. 2012).

4. PTO's SUMF ¶¶ 4 -5. Each alleged fact is disputed to the extent this statement is taken out of context or purports to set forth all of the disclosures made in the '171 Application. Disputed on relevance in that for obviousness type double patenting, reference to the specification is limited primarily to claim construction and this alleged fact is not being proffered for that purpose. *See Eli Lilly*, 689 F.3d at 1380.

5. PTO's SUMF ¶ 6. Disputed to the extent this statement is taken out of context or

purports to set forth all of the disclosures made in the '171 Application. The first quote is taken out of context, incomplete and omits the last part of the sentence that shows it relates to sHASEGP's, which is not the scope of the subject matter claimed. (A1831, Abstract.) Moreover, to the extent proffered for claim construction, the statement is directed to the distinct claim term "pharmaceutical carrier" and not to the claim term "pharmaceutical composition" or "the composition is formulated for systemic administration."

6. PTO's SUMF ¶¶ 7-8. Each alleged fact is disputed to the extent this statement is taken out of context or purports to set forth all of the disclosures made in the '171 Application. Disputed on relevance in that for obviousness type double patenting, reference to the specification is limited primarily to claim construction and this alleged fact is not being proffered for that purpose. *See Eli Lilly*, 689 F.3d at 1380.

7. PTO's SUMF ¶ 9. Disputed to the extent this statement is taken out of context or purports to set forth all of the disclosures made in the '171 Application. The first quote is taken out of context, incomplete and omits the last part of the sentence that shows it relates to sHASEGP's, which is not the scope of the subject matter claimed. (A1831, Abstract.) Disputed on relevance in that for obviousness type double patenting, reference to the specification is limited primarily to claim construction and this alleged fact is not being proffered for that purpose. *See Eli Lilly*, 689 F.3d at 1380. Moreover, to the extent proffered for claim construction, the statement is directed to the distinct claim term "pharmaceutical carrier" and not "pharmaceutical composition" or "the composition is formulated for systemic administration."

8. PTO's SUMF ¶¶ 10-17. Undisputed.

9. PTO's SUMF ¶ 18. Disputed. The statements are taken out of context, incomplete and omit disclosures that contradict the PTO's assertions. Disputed on relevance in

that for obviousness type double patenting, reference to the specification is limited primarily to claim construction and this alleged fact is not being proffered for that purpose. *See Eli Lilly*, 689 F.3d at 1380. The first quote omits the last part of the sentence: "discovery of novel soluble neutral active Hyaluronidase Glycoproteins (sHASEGP's), methods of manufacture, and their use to facilitate administration of other molecules *or to alleviate glycosaminoglycan associated pathologies*. (A1629, Abstract (emphasis added).) The second sentence is also taken out of context by omitting other forms of recombinant sHASEGPs. (*Id*.)

10. PTO's SUMF ¶ 19. Disputed. Disputed on relevance in that for obviousness type double patenting, reference to the specification is limited primarily to claim construction and this alleged fact is not being proffered for that purpose. *See Eli Lilly*, 689 F.3d at 1380. Moreover, to the extent proffered for claim construction, the statement is directed to the distinct claim term "pharmaceutical carrier" and not "pharmaceutical composition" or "the composition is formulated for systemic administration." The first quote is taken out of context, incomplete and omits the last part of the sentence that shows it relates to sHASEGP's, which is not the scope of the subject matter claimed. (A1831, Abstract.) The cited portions of the specification are disclosures related to sHASEGPs, not PEGylated forms of recombinant sHASEGPs. (*See* A1642, 1:1927, A1645, 8:14-21 and A1668-A1669, 54:66-55:3.)

11. PTO's SUMF ¶¶ 20-23. Undisputed.

12. PTO's SUMF ¶ 24. Disputed. Disputed on relevance in that for obviousness type double patenting, reference to the specification is limited primarily to claim construction and this alleged fact is not being proffered for that purpose. *See Eli Lilly*, 689 F.3d at 1380. Moreover, to the extent proffered for claim construction, the statement is directed to the distinct claim term "pharmaceutical carrier" and not "pharmaceutical composition" or "the composition is

formulated for systemic administration." The first quote is taken out of context, incomplete and omits the last part of the sentence that shows it relates to sHASEGP's, which is not the scope of the subject matter claimed. (A1831, Abstract.)

13. PTO's SUMF ¶ 25. Disputed on relevance in that for obviousness type double patenting, reference to the specification is limited primarily to claim construction and this alleged fact is not being proffered for that purpose. *See Eli Lilly*, 689 F.3d at 1380. Disputed to the extent this statement is taken out of context incomplete and purports to set forth all of the disclosures made in the summary of the invention of the '431 Patent, which spans over 10 pages. (A1844-A1854.)

14. PTO's SUMF ¶ 26. Disputed to the extent this statement is taken out of context, incomplete and purports to set forth all of the disclosures made in the examples of the '431 Patent. Example 21 does not disclose a pharmaceutical composition comprising a PEGylated rHuPH20 *and* insulin and thus reference to this section of the specification for ODP is incorrect. (A1912-A1913, Example 21.)

15. PTO's SUMF ¶¶ 27-29. Undisputed.

16. PTO's SUMF ¶ 30. Disputed. Disputed on relevance in that for obviousness type double patenting, reference to the specification is limited primarily to claim construction and this alleged fact is not being proffered for that purpose. *See Eli Lilly*, 689 F.3d at 1380. Moreover, to the extent proffered for claim construction, the statement is directed to the distinct claim term "pharmaceutical carrier" and not "pharmaceutical composition" or "the composition is formulated for systemic administration." The first quote is taken out of context, incomplete and omits the last part of the sentence that shows it relates to sHASEGP's, which is not the scope of the subject matter claimed. (A1831, Abstract.)

17. PTO's SUMF ¶¶ 31-33. Undisputed.

18. PTO's SUMF ¶ 34. Disputed. The correct U.S. Patent No. is 5,766,897 to Braxton ("Braxton") and is titled "Cysteine-Pegylated Proteins." (A1547.) The Abstract states that "[m]ethods and compositions are provided for the production of PEGylated proteins having polyethylene glycol covalently bound to a cysteine residue present in either the naturally-occurring protein or introduced by site-specific mutation . . . [t]he modified proteins produced by the method of the invention are referred to as cysteine-PEGylated proteins." (A1547, Abstract (emphasis added).) One of skill reading Braxton would not agree that Braxton is "generally directed to the production of PEGylated proteins." (Ex. A, Ex. 47, Corr. Flamion Rep., ¶ 105; Ex. A, Ex. 1, Corr. Zalipsky Rep., ¶¶ 108-113.)

19. PTO's SUMF ¶ 35. Disputed. Braxton teaches that proteins PEGylated using site specific conjugation to cysteine residues (the invention claimed therein) have certain properties, not generally as the alleged fact states. The quotes are taken out of context, incomplete and omits this key point of the invention that is tied to cysteine conjugation on the protein, as the full cites demonstrate, *e.g.*:

> The invention relates to **identifying cysteine residues, or amino acid residues which may be substituted by cysteine, and attaching polyethylene glycol to the thio group of cysteine**, thereby increasing protein stability without abolishing biological activity.

(A1556, 1:20-25 (emphasis added); *see also* A1560, 10:26-52; Ex. A, Ex. 1, Corr. Zalipsky Rep., ¶¶ 108-113; Ex. A, Ex. 47, Corr. Flamion Rep., ¶¶ 105-108; Ex. A, Ex. 86, Zalipsky Rebuttal Rep., ¶¶ 69, 72; Ex. A, Ex. 101, Flamion Rebuttal Rep., ¶ 61.)

20. PTO's SUMF ¶ 36. Disputed. Braxton's teachings focus on smaller molecular weight proteins that have a different mechanism of clearance from the larger human-derived hyaluronidase of the claimed invention. The first quote is taken out of context and incomplete in

that the next sentence goes on to explain that the short half-life is due to kidney clearance: "Most proteins, particularly relatively low molecular weight proteins introduced into the circulation, are cleared quickly from the mammalian subject by the kidneys." (A1556:48-51 (emphasis added).) The second quote is also taken out of context and incomplete as Braxton qualifies that "modification of the therapeutic protein by covalent attachment of polyalkylene oxide polymers, particularly polyethylene glycols (PEG)" is the most promising of the approaches "to date." (A1556:1:63-66). Further, that "[a]ttempts such as [PEGylated adenosine deamidase, L-asparaginase, interferon alpha 2b, superoxide dismutase, streptokinase, tissue plasminogen activator, urokinase, uricase, hemoglobin, interleukins, interferons, TGF-β, and other growth factors] have resulted in somewhat longer half-life of the proteins and reduction of protein immunogenicity." (A1556:2:4-11; *see also*; Ex. A, Ex. 1, Corr. Zalipsky Rep., ¶¶ 108-113; Ex. A, Ex. 47, Corr. Flamion Rep., ¶ 107; Ex. A, Ex. 86, Zalipsky Rebuttal Rep., ¶ 97; Ex. A, Ex. 101, Flamion Rebuttal Rep., ¶ 61.)

21. PTO's SUMF ¶ 37. Disputed. The quotes are taken out of context, incomplete and omit disclosures that contradict the PTO's assertions. Braxton discourages the method, *i.e.*, random, multi-PEGylation of the lysine residues, employed by Halozyme in PEGylating its human-derived hyaluronidase of the claimed invention by teaching that PEGylating lysine residues is random and "result[s] in the production of a heterogeneous mixture of PEGylated proteins which differ in both the number and position of PEG groups attached" rendering "[s]uch mixtures of diversely modified proteins [] not suitable as pharmaceutical compositions." (A1556, 2:23-34 (emphasis added).) The express claim language in the '171 Application is directed to "a pharmaceutical composition," confirming how one of skill would understand Braxton to teach away from the claimed inventions because lysine conjugation is "not suitable"

for pharmaceutical compositions. Braxton also notes that while there are several other methods for protein modification with PEG through free lysine residues, "each suffers from the problems associated with partial, random modification of protein and the potential for losing activity if lysine residues are essential for biological activity." (A1556, 2:60-65; Ex. A, Ex. 1, Corr. Zalipsky Rep., ¶ 118; Ex. A, Ex. 47, Corr. Flamion Rep., ¶ 108; Ex. A, Ex. 86, Zalipsky Rebuttal Rep., ¶ 70; Ex. A, Ex. 101, Flamion Rebuttal Rep., ¶ 61.)

22. PTO's SUMF ¶ 38. Disputed. The quotes are taken out of context, incomplete and omit disclosures that contradict the PTO's assertions. Braxton goes on to suggest that the "ratio of PEG to protein is preferably 1:1, more preferably 2:1, even more preferably 5:1, up to 10:1 or 40:1 ratio of PEG molecules to protein." (A1562, 13:4-7.) Braxton also teaches that the "actual number of PEG molecules covalently bound per chemically modified protein of the invention may vary widely depending upon the desired protein stability (*e.g.*, serum half-life) and the protein used for chemical modification." (A1561, 12:55-59 (emphasis added).) Further, the chemically modified proteins of the Braxton invention relate specifically to cysteine-PEGylated proteins. (Halozyme Response to PTO's SUMF, ¶¶ 34-35.) Braxton also states that "[p]referably the chemically modified protein composition produced by the subject invention will be homogenous with respect to the position of the cysteine residue(s) modified and the number of cysteine residue(s) modified." (A1562, 13:7-10.) The goal of utilizing site-specificity is to attach one or at best, two PEGs, at sites where they are beneficial and do not adversely affect properties of the conjugate. (Ex. A, Ex. 1, Corr. Zalipsky Rep., ¶ 116; Ex. A, Ex. 86, Zalipsky Rebuttal Rep., ¶ 72; Ex. A, Ex. 95, Vanwetswinkel 2000; Ex. A, Ex. 98, Mei 2010; and Ex. A, Ex. 100, Xu 2013.) Thus, the higher ratios of PEG, *i.e.*, introduction of multiple cysteines to a protein for the purpose of PEGylation, is counterproductive with the intent and goals of

Braxton, because as multiple cysteines are introduced, it is likely to lead to heterogeneous, improperly folded, and inactive protein aggregates. (*Id.*)

23. PTO's SUMF ¶ 39. Disputed. The correct U.S. Patent No. is 6,552,170 to Thompson et al. ("Thompson") and is titled "Pegylation Reagents and Compounds Formed Therewith." (A1596.) Thompson teaches making a "dumbbell" conjugate with a bivalent PEG in-between two proteins as illustrated by the Abstract which states that "[c]ompounds are disclosed having the general formula R1-X-R2, wherein R1 and R2 are biologically active groups, at least one of which is a polypeptide." (A1596, Abstract.) PEG serves as a spacer in these constructs, not a properties modifier. (Ex. A, Ex. 1, Corr. Zalipsky Rep., ¶ 121; Ex. A, Ex. 86, Zalipsky Rebuttal Rep., ¶ 76.)

24. PTO's SUMF ¶ 40. Disputed to the extent this statement is taken out of context and incomplete. Thompson's teachings focus on smaller molecular weight proteins that have a different mechanism of clearance from the larger human-derived hyaluronidase of the claimed invention. Thompson explains that "[u]p to a certain size, the rate of glomerular filtration of proteins is inversely proportional to the size of the protein. The ability of PEGylation to decrease clearance, therefore, is generally not a function of how many PEG groups are attached to the protein, but the overall molecular weight of the altered protein." (A1602, 1:61-66.) These teachings are irrelevant to the claimed human-derived hyaluronidase because the unique structure plays a critical role in clearance of the enzyme rather than its overall molecular weight, and further does not pose immunogenicity problems because it is human. (Ex. A, Ex. 1, Corr. Zalipsky Rep., ¶¶ 128-129, 164-165; Ex. A, Ex. 86, Zalipsky Rebuttal Rep., ¶ 77; Ex. A, Ex. 24, Knauf 1988; Ex. A, Ex. 20, Zalipsky 1995; Ex. A, Ex. 17, Chiu 1993; Ex. A, Ex. 15, Zalipsky 1992; Ex. A, Ex. 27, Nodake 2000; Ex. A, Ex. 41, Zalipsky 2007; Ex. A, Ex. 16, Matsuyama

1992; Ex. A, Ex. 36, Sakakibara 2002; Ex. A, Ex. 11, Caliceti 1990.)

25. PTO's SUMF ¶ 41. Disputed. The quotes are taken out of context, incomplete and omit disclosures that contradict the PTO's assertions. In fact, Thompson, like Braxton, highlights the problems associated with non-specific PEGylation at lysine residues:

> PEGylation of proteins illustrates some of the problems that have been encountered in attaching PEG to surfaces and molecules. The vast majority of PEGylating reagents react with free primary amino groups of the polypeptide. Most of these free amines are the epsilon amino group of lysine amino acid residues. Typical proteins possess a large number of lysines. Consequently, **random attachment of multiple PEG molecules often occurs leading to loss of protein activity**.
>
> In addition, **if the PEGylated protein is intended for therapeutic use, the multiple species mixture that results from the use of non-specific PEGylation leads to difficulties in the preparation of a product with reproducible and characterizable properties**. This **non-specific PEGylation makes it difficult to evaluate therapeutics and to establish efficacy** and dosing information. The site selective PEGylation of such proteins could lead to reproducibly-modified materials that gain the desirable attributes of PEGylation without the loss of activity.

(A1602, 2:10-28 (emphasis added).) Thompson teaches site-specific, mono-PEGylation at the cysteine residues. (*See* A1605, 7:12-15, A1605, 7:15-17, A1603, 3:42-55 and A1604, 6:42-43; Ex. A, Ex. 1, Corr. Zalipsky Rep., ¶¶ 126-127; Ex. A, Ex. 47, Corr. Flamion Rep., ¶ 108; Ex. A, Ex. 86, Zalipsky Rebuttal Rep., ¶¶ 78-79; Ex. A, Ex. 101, Flamion Rebuttal Rep. ¶ 61.)

26. PTO's SUMF ¶ 42. Undisputed, but incomplete.

27. PTO's SUMF ¶ 43. Disputed to the extent this statement is taken out of context, incomplete and inconsistent with the administrative record by purporting to set forth all of the arguments Halozyme made in its appeal to the PTAB. Halozyme also argued that the claims are directed to a pharmaceutical composition that is formulated for systemic administration and particular human-derived hyaluronidases of specific sequences. (A1240-A1246.) This statement constitutes an accurate characterization of the administrative record in this action.

28. PTO's SUMF ¶ 44. Disputed in that this statement constitutes a characterization of the administrative record in this action. Disputed also as to the ultimate conclusion of obviousness-type double patenting.

29. PTO's SUMF ¶¶ 45-47. Each alleged fact is disputed to the extent the statement is inconsistent with the administrative record. Disputed also as to the ultimate conclusion of obviousness-type double patenting. Halozyme has presented new evidence and expert testimony disputing the Examiner and PTAB's findings as explained below in Response to SUMF 48.

30. PTO's SUMF ¶ 48. Disputed. Halozyme presented new evidence in this action, including: testimony relating to the development, marketing, licensing and commercialization of the '171 Application by Dr. Michael LaBarre, Halozyme's Chief Scientific Officer; testimony by an inventor of the '171 Application, Dr. Gregory I. Frost; expert testimony by Drs. Samuel Zalipsky and Bruno Flamion relating to the nonobviousness of the '171 Application as viewed from the perspective of one of ordinary skill in the art, including the scope and content of the prior art, the differences between the claims and the prior art, the level of ordinary skill in the art, objective considerations of nonobviousness, rebuttal of the obviousness-type double patenting rejections by the Examiner and PTAB, and testimony on each factual finding by the PTAB; expert testimony by Jon Saxe regarding commercial success, one objective consideration of nonobviousness; prior art publications; laboratory notebooks; portions of Halozyme's IND submission; third party research and collaboration agreements; SEC filings; press releases; and Halozyme corporate presentations. (*See, e.g.*, ECF No. 77, Plaintiff Halozyme's Rule 26(a)(3) Pretrial Disclosures; *see also* Ex. A, Exs. 1-106, 108, 110, 112-114, 123; Ex. B, Exs 1-12.)

LEGAL PRINCIPLES

I. STANDARD OF REVIEW FOR SECTION 145 ACTION AND SUMMARY JUDGMENT

A plaintiff in a civil action under 35 U.S.C. § 145 is "free to introduce new evidence in Section 145 proceedings subject only to the rules applicable to all civil actions, the Federal Rules of Evidence and the Federal Rules of Civil Procedure." *Kappos v. Hyatt*, 132 S. Ct. 1690, 1700 (2012) (rejecting PTO argument that challenged administrative record is entitled to deference).[1] "[I]f new evidence is presented on a disputed question of fact, the district court must make *de novo* factual findings that take account of both the new evidence and the administrative record before the PTO. *Id.* at 1701*; see also id. at 1696* (rejecting "deferential standard of review" of PTAB decision in Section 145 action); *see also BTG Int'l Ltd. v. Kappos*, No. 1:12-CV-682, 2012 WL 6082910, at *4 (E.D.Va., Dec. 6, 2012) (quoting *Kappos v. Hyatt*). Applicant may raise new issues not raised or considered by the USPTO or by the PTAB. *Disney Enterprises, Inc. v. Kappos*, 923 F. Supp.2d 788, 802 (E.D.Va., 2013).

When a motion for summary judgment is under consideration, "[t]he evidence of the nonmovant is to be believed, and all justifiable inferences are to be drawn in his favor." *Anderson v. Liberty Lobby, Inc.*, 477 U.S. 242, 255 (1986). The Court's function is not "to weigh the evidence and determine the truth of the matter but to determine whether there is a

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[1] 35 U.S.C. § 145 provides:

> [a]n applicant dissatisfied with the decision of the Patent Trial and Appeal Board in an appeal under section 134(a), may…have remedy by civil action against the Director in the United States District Court for the Eastern District of Virginia...The court may adjudge that such applicant is entitled to receive a patent for his invention, as specified in any of his claims involved in the decision of the [USPTO], as the facts in the case may appear and such adjudication shall authorize the Director to issue such patent on compliance with the requirements of law.

genuine issue for trial." *Id.* at 249. The inquiry is "whether the evidence presents a sufficient disagreement to require submission to a jury or whether it is so one-sided that one party must prevail as a matter of law." *Id.* at 251.

ARGUMENT

II. HALOZYME IS ENTITLED TO PARTIAL SUMMARY JUDGMENT THAT THE PENDING CLAIMS ARE NOT OBVIOUS UNDER 35 U.S.C. § 103 OVER BOOKBINDER IN VIEW OF BRAXTON AND THOMPSON

It is well-settled that one's own invention, whatever form of disclosure to the public, may not be prior art against oneself, absent a statutory time bar. 35 U.S.C. § 102 (a) & (e); *In re Katz*, 687 F.2d 450, 454 (Fed. Cir. 1982). The PTO agreed in interrogatory responses, stating that if the claims are entitled to the priority date of February 23, 2005, Bookbinder may be prior art only if it is by "another." (Ex. 107, Def. Third Supp Response to 1st Set of Interrogs, p. 7.)

Here, the evidence is undisputed. Priority of the Pending Claims to the February 23, 2005 '716 Application is established because (a) Halozyme affirmatively showed written description and enablement support for the Pending Claims and (b) the PTO by Interrogatory Responses never contested or raised lack of written description or enablement for the Pending Claims to the '716 Application.[2] (Ex. A, Ex. 86, Zalipsky Rebuttal Rep. ¶¶ 53-54.) The three named inventors are the same on Bookbinder patent application as the '171 Application, *i.e.,* Louis Bookbinder, Anirban Kundu, and Gregory Frost. (Halozyme SUMF ¶¶ 5-9.) The Bookbinder patent application is not be "another" and therefore is not prior art to the Pending Claims.

The PTAB's first ground for decision that has been appealed is plainly erroneous, namely

[2] When a party seeks the benefit of an earlier-filed United States patent application, the earlier application must meet the requirements of 35 U.S.C. § 120 and 35 U.S.C. § 112 ¶ 1, which means the earlier application must contain a written description of the subject matter and must meet the enablement requirement. *See Hyatt v. Boone*, 146 F.3d 1348, 1352 (Fed. Cir. 1998).

that the Pending Claims under 35 U.S.C. § 103 as unpatentable over Bookbinder, Braxton, and Thompson where Bookbinder does not legally qualify as Section 102 prior art that may be used for purposes of Section 103. Partial Summary Judgment should be granted against the PTO.

III. THE PTO'S MOTION FOR SUMMARY JUDGMENT CANNOT BE GRANTED BECAUSE THERE ARE MATERIAL FACTS IN GENUINE DISPUTE

A. OBVIOUSNESS TYPE DOUBLE PATENTING LEGAL STANDARDS

The judicially-created doctrine of obviousness-type double patenting is intended to "prevent the extension of the term of a patent . . . by prohibiting the issuance of the claims in a second patent not patentably distinct from the claims of the first patent." *Eli Lilly*, 689 F.3d at 1376. The obviousness-type double patenting inquiry consists of two steps: "First, the court construes the claim[s] in the earlier patent and the claim[s] in the later patent and determines the differences. Second, the court determines whether those differences render the claims patentably distinct." *AbbVie Inc. v. Mathilda & Terence Kennedy Inst. Rheumatology Trust*, 764 F.3d 1366, 1373 (Fed. Cir. 2014).

The second step "of the obviousness-type double patenting analysis is analogous to an obviousness analysis under 35 U.S.C. § 103." *Id.* at 1378. As the PTO acknowledges, while the ultimate question of obviousness under 35 U.S.C. § 103 is a matter of law, this determination rests on several factual inquires, including: "(1) the scope and content of the prior art; (2) the differences between the claims and the prior art; (3) the level of ordinary skill in the art; and (4) objective considerations of nonobviousness." *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966); PTO Br. at p. 16.[3]

In assessing the patentable distinction, "the claims must be considered as a whole," *i.e.*,

[3] The obviousness inquiry is made from the perspective of a person of ordinary skill in the art at the time of the invention. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007).

the district court should "examin[e] whether one of ordinary skill in the art would have been motivated to modify the [reference] Compound to create [the compound of the asserted claim], considering the compounds as a whole." *Eli Lilly,*, 689 F.3d at 1377.

B. GENUINE DISPUTE OF MATERIAL FACTS EXIST WITH REGARD TO THE AGENCY'S OBVIOUSNESS TYPE DOUBLE PATENTING REJECTIONS OF THE PENDING CLAIMS BASED ON CLAIMS 9 AND 10 OF U.S. PATENT NO. 7,767,429 IN VIEW OF BRAXTON AND THOMPSON

1. The PTO's Motion Fails To Properly Construe Claim 264's Terms "Pharmaceutical Composition" and "the Composition Is Formulated for Systemic Administration" and Instead Incorrectly Relies on the Distinct Claim Term "Pharmaceutically Acceptable Carrier"

Turning first to claim construction – a step the PTO glosses over – it is readily apparent that there are several material claim term differences between the claims. Claim 264[4] of the '171 Application, upon which Pending Claims 295-298, 300 and 303 depend, contrasts to Claim 10 of the '429 Patent as follows:[5]

Pending Claim 264, '171 Application	Claim 10, '429 Patent
264. A *pharmaceutical composition*, comprising a PEGylated hyaluronidase in a *pharmaceutically acceptable carrier*, wherein:	
	10. The hyaluronidase glycoprotein of claim 9, wherein the polymer is PEG or dextran. 9. The hyaluronidase glycoprotein of claim 7, wherein the hyaluronidase glycoprotein is modified with a polymer.
the hyaluronidase contains about three to six PEG moieties per hyaluronidase molecule	
the hyaluronidase polypeptide is a human-	7. A substantially purified hyaluronidase

[4] To streamline this proceeding, Halozyme narrowed the appealed claims to Claims 295-298, 300 and 303. As they depend on Claim 264, the limitations of Claim 264 are incorporated into the pending appealed claims.

[5] Claim 10 of the '429 Patent is dependent on Claim 9, which is dependent on Claim 7 of the '429 Patent. Accordingly, all three claims are considered in Halozyme's analysis of obviousness-type double patenting of Claim 10.

derived hyaluronidase	glycoprotein, wherein the hyaluronidase glycoprotein: is soluble; is neutral active; contains at least one sugar moiety that is covalently attached to an asparagine (N) residue of the polypeptide; and consists of the sequence of amino acids set forth as amino acids 36-477, 36-478, 36-479, 36-480, 36-481, 36-482, or 36-483 set forth in SEQ ID NO:1 or contains amino acid substitutions in the sequence of amino acids set forth as amino acids 36-477, 36-478, 36-479, 36-480, 36-481, 36-482, or 36-483 of SEQ ID NO:1, whereby the amino-acid substituted hyaluronidase glycoprotein consists of a sequence of amino acids that has at least 95% amino acid sequence identity with the sequence of amino acids set forth as amino acids 36-477, 36-478, 36-479, 36-480, 36-481, 36-482, or 36-483 of SEQ ID NO:1.
and ***the composition is formulated for*** *systemic administration*	

(SUF, ECF No. 76, ¶¶ 7(a); 9-12 (emphasis added).)

Claim 264 plainly requires a *pharmaceutical* composition containing a specifically "formulated" human derived hyaluronidase of *three to six PEGs* for *systemic administration*. Properly construed as read by one of ordinary skill, those limitations in combination convey to one of ordinary skill in the art that there must be a suitable serum half-life and activity for the pharmaceutical composition to be used for systemic administration. (Ex. A, Ex. 1, Corr. Zalipsky Rep. ¶ 186; Ex. A, Ex. 86, Zalipsky Rebuttal Rep., ¶¶ 89, 117-118; Ex. A, Ex. 47, Corr. Flamion Rep., ¶¶ 92, 114; Ex. A, Ex. 101, Flamion Rebuttal Rep., ¶¶ 54, 59-60, 82; Ex. A, Ex. 108, Flamion Tr., 131:6-17, 133:6-134:3.)

In ODP claim construction, the actual language of the claims as understood by one of skill is paramount, but the specification may be consulted for the limited purpose of construing limitations found in the claims. *Eli Lilly*, 689 F.3d at 1380. The PTO incorrectly collapses the first construction step into its "patentably indistinct" arguments, and in doing so, advances

several erroneous statements that do not withstand scrutiny.

First, read as a whole by one of skill, the claim 264 language reveals that the preamble's phrase "pharmaceutical composition" is carried into the body of the claim by the claim limitation that "***the composition*** is formulated for systemic administration." This plainly refers to the antecedent "pharmaceutical composition" in the preamble. Therefore, the PTO *errs* in arguing that the term "pharmaceutical composition" is just "preamble language" that "is *not* limiting." PTO Br. at 22. It is in the body of the claim and therefore is limiting.

Second, Claim 264 distinguishes between the "*pharmaceutical composition*" and the separate claim term "in a *pharmaceutically-acceptable carrier*." The PTO incorrectly attempts to water down the claim by referring to the distinct claim language of a "*pharmaceutically-acceptable carrier*" and pointing to language in the specification relating to "carriers." *See* PTO Br. at 23-24."[6] But that is error as the claim language "pharmaceutical composition" differs from "pharmaceutically-acceptable carrier."

Third, the '171 Application's specification teaches that the specifically formulated human hyaluronidase with about three to six PEG moieties, as a pharmaceutical composition for use in systemic administration, has a serum "half-life" and "activity," as *plainly disclosed in the specification's example 21A*. (Ex. A, Ex. 1, Corr. Zalipsky Expert Rep., ¶ 80 (Example 21-A further teaches that "PEGylation with three to six PEG moieties improved half-life 16-20 fold" and was sufficient to "retain activity to provide a therapeutic effect.).) This example in the specification supports Halozyme's construction. Reading the claim as the PTO does, is *explicitly contrary* to the specification's example that shows activity and serum half-life.

[6] As further discussed, *infra*, the PTO further errs by pointing to the specification of the '429 Patent for determining the patentable distinctiveness between the claims.

Fourth, the teachings of the specification as read by one of ordinary s are that one of skill would understand that the Claim 264's "limitations of 'pharmaceutical composition' and formulated for 'systemic administration,' along with the intended utility, all illustrate that level of serum half-life and therapeutic effect at the distal tissues are limitations of the inventions claimed." (Ex. A, Ex. 101, Flamion Rebuttal Rep., ¶ 19; Ex. A, Ex. 86, Zalipsky Rebuttal Rep., ¶ 30.)

Fifth, the Claim 264 terms "pharmaceutical composition," "the hyaluronidase contains about three to six PEG moieties per hyaluronidase molecule," and "the composition is formulated for systemic administration" are not present in the '429 Patent claims. Thus, any attempt to attach or read in those limitations in the proper construction of Claims 9 and 10 of the '429 Patent would be error. The PTO recognizes this basic principle in MPEP 804.II.B.2.(a): "Subject matter disclosed in the reference patent [(here the '429 Patent)] or application that does not fall within the scope of a reference claim cannot be used to construe the claim in the context of a nonstatutory double patenting analysis as this would effectively be treating the disclosure as prior art."

2. The '171 Application Claim 264 and the '429 Patent Claims 9 and 10 Are Patentably Distinct

The difference between the claims is apparent.

- Claim 264 claims a **pharmaceutical composition that is formulated for systemic administration** that includes a **specific human derived hyaluronidase containing about three to six PEG moieties per hyaluronidase molecule**.[7]

[7] Claims 295-298, 300 and 303 further claim specific amino acid sequences of the human derived hyaluronidase – a further point of distinction when the claims are read as a whole. The PTO argues that because these sequences fall within ranges recited in Claim 10 of the '429 Patent, that there is no patentable distinction. PTO Br. at 25-26. Again, this reasoning is misplaced because the claims must be read as a whole. As a whole, the pending claims recite a specific species of human-hyaluronidase with about three to six PEG moieties that is a pharmaceutical composition formulated for systemic administration.

- By contrast, Claim 10 of the '429 Patent claims **a compound** of human-derived hyaluronidase that is modified by a polymer, including **any PEG or any dextran molecule, without limitation as to number, or whether** such modification is suitable for a pharmaceutical composition to be used for systemic administration.

These differences render the claims patentability distinct or at a minimum, raise triable issues, *infra*. Moreover, these differences are to be assessed as a whole in the context of all claim elements. *See Eli Lilly*, 689 F.3d 1368 at 1377 ("so too must the subject matter of the [] claims be considered 'as a whole' to determine whether the [] Compound would have made those claims obvious for purposes of obviousness-type double patenting.")

(a) The State of the Art Shows That There Was Great Uncertainty To Motivate and Have a Reasonable Expectation of Success To Achieve a Pharmaceutical Composition of Three to Six PEGs to the Specific Human Hyaluronidase for Systemic Use

The PTO fails to address the material evidence Halozyme has advanced, relying on the same flawed analysis by the PTAB that did not have any evidence put before it. There are at least two overarching factual areas that the PTO's motion fails to address:

- Halozyme's experts show that the general state of the art on PEGylating for achieving "the balance of sufficient enzymatic activity and prolonged circulation for enzymes that act on macromolecular substrates (such as hyaluronidase) was, and continues to remain very challenging with a low expectation of success, particularly by nonspecific amine-directed PEGylation. (Ex. A, Ex. 1, Corr. Zalipsky Rep., Sections V.C and VIII.D.2.; Ex. A, Ex. 86, Zalipsky Rebuttal Rep., ¶¶ 48, 87.)

- Compounding the issue, as Halozyme's experts show, this specific protein, human-derived hyaluronidase, is a virtually-unique glycoprotein that presents specific issues on whether one of skill would be motivated to PEGylate it with three to six PEG moieties to be used in a systemic administration where activity must be achieved at distal tissues, much less have a reasonable expectation of success. (Ex. A, Ex. 47, Corr. Flamion Rep., Section V.A and B; Ex. A, Ex. 101, Flamion Rebuttal Rep., Section B; Ex. A, Ex. 1, Corr. Zalipsky Rep., Section VIII.C and D; Ex. A, Ex. 86, Zalipsky Rebuttal Rep., Section VIII.B.1.) In other words, put simply, it was no simple matter to successfully make this human derived hyaluronidase with about three to six PEG moieties for use in a systemic application that would have suitable activity and half-life in the body to reach the distal tissues, as the Inventor also testified. (Ex. A, Ex. 113, Frost Tr., 40:1-46:20, 100:17-106:6, 107:15-117:8.)

There is no real dispute on these general points. The PTO's expert Dr. Zhou agreed, testifying that protein modification "*is very specific to each protein*," and "[*t]here is lots of box to check*." (Ex. A, Ex. 109, Zhou Tr., 85:15-25; 126:20-127:5 (emphasis added)); *see UCB, Inc. v. Accord Healthcare, Inc.*, 201 F.Supp.3d 491, 532 (D. Del. 2016) ("given how unpredictable drug development is [ ], and the high likelihood that any formulation will prove unsuccessful [ ], the lack of data strongly contributes to the Court's finding that . . . the asserted claims [(are)] patentably distinct. *It is only with improper use of hindsight that one could conclude that it would have been obvious to a POSA to use those structures to fill in the variables*.")

(b) The Evidence Shows that the Braxton and Thompson References Do Not Supply the Range, Motivation or Reasonable Expectation of Success

The PTO argues that the PTAB properly relied on the Braxton and Thompson references to supply (i) the 3-6 PEG claim elements, (ii) motivation to combine and (iii) reasonable expectation of success. At the outset, the need for additional references is an admission that the Pending Claims are not patentably indistinct in view of the '429 Patent claims *alone*.

More importantly, page after page of Halozyme's expert reports explained why the PTAB's reliance on Braxton and Thompson to supply these necessary elements was misplaced. (Halozyme's Response to PTO's SUMF ¶¶ 35, 41; Ex. A, Ex. 1, Corr. Zalipsky Rep., Section VIII; Ex. A, Ex. 47, Corr. Flamion Rep., Section V; Ex. A, Ex. 86, Zalipsky Rebuttal Rep., ¶¶ 82-88; 116-118; Ex. A, Ex. 101, Flamion Rebuttal Rep., ¶ 61.)

At its core, the PTAB erred by failing to appreciate that one of ordinary skill would understand that Braxton and Thompson teach PEG conjugations to cysteine amino acids that if done with human-derived hyaluronidase, would likely *destroy* the requisite activity of the

human-derived hyaluronidase, rendering it inoperable.[8] (Ex. A, Ex. 1, Corr. Zalipsky Rep., ¶ 111-113, 116; 124, 155, 159, 166, 170, 187; Ex. A, Ex. 47, Corr. Flamion Rep., ¶¶ 79-85, 105, 119; Ex. A, Ex. 31, Li 2002; Ex. A, Ex. 65, Markovic-Housley 2000; Ex. A, Ex. 72, Skov 2006; Ex. A, Ex. 75, Chao 2007; Ex. A, Ex. 83, Meschach 2017; Ex. A, Ex. 60, Hunnicutt 1996; Ex. A, Ex. 69, Chowpongpang 2004.)

The PTO does not dispute this point and instead, contends that it is irrelevant that Braxton and Thompson teach site-specific cysteine PEGylation techniques because "they also explain that lysine (amine) PEGylation was the most popular and widespread method" and a skilled artisan recognizing that cysteine PEGylation was not practical for the claimed hyaluronidases, "would naturally have turned to lysine (amine) PEGylation." PTO Br. at 19.

Not so. Braxton states that the lysine approach "*suffers from the problems associated with partial, random modification of protein and* ***the potential for losing activity*** *if lysine residues are essential for biological activity.*" (A1556, 2:62-65.) Halozyme's experts will testify that a person of ordinary skill in the art would have read Braxton and Thompson as *discouraging* one of ordinary skill in the art from being motivated to use non-specific PEGylation at the lysine residues for proteins intended for therapeutic use as pharmaceutical compositions, much less having a reasonable expectation of success. *Millennium Pharmaceuticals, Inc. v. Sandoz Inc.*, 862 F.3d 1356, 1366 (Fed. Cir. 2017) ("A reference may be said to teach away when a person of

[8] Further, that Braxton and Thompson's preference for mono-PEGylation at the cysteine residues teach away from the about three to six PEG moieties as required in Pending Claim 264. (Ex. A, Ex. 86, Zalipsky Rebuttal Rep., ¶ 116.) Finally, Thompson teaches making a "dumbbell" conjugate of a R1-PEG-R2 structure where PEG serves as a spacer in these "dumbbell" constructs, not a properties modifier, like in the claimed invention of the '171 Application. (Halozyme's Response to PTO's SUMF ¶ 39; Ex. A, Ex. 86, Zalipsky Rebuttal Rep., ¶ 76.) Notably, the PTO's motion only in passing references Thompson, highlighting the lack of merit for Thompson to serve as a legitimate secondary reference.

ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant."). (*See* Halozyme's Response to the PTO's SUMF, ¶¶ 37, 41; Ex. A, Ex. 86, Zalipsky Rebuttal Rep., ¶¶ 70, 79, 82; Ex. A, Ex. 101, Flamion Rebuttal Rep., ¶ 61.) This is not "beside the point," as the PTO incorrectly contends: it goes to the very heart of the factual dispute and is directly disputed. PTO Br. at 19.[9] *See Para-Ordinance Mfg., Inc. v. SGS Imp. Int'l, Inc.*, 73 F.3d 1085, 1088 (Fed. Cir. 1995) (what a prior art reference discloses is a *factual inquiry*).

The PTO further contends that Braxton discloses the specific range of PEG moieties. PTO Br. at 19. But again, the PTO turns a blind eye to the evidence. Halozyme's experts opine that one of skill reading Braxton would understand that range to provide no more than a generalized teaching that is inapplicable to this specific protein. (Halozyme's Response to PTO's SUMF ¶ 38.) In fact, as the PTO's expert Dr. Zhou admitted, that section of the Braxton specification relates to cysteine conjugation, not lysine conjugation. (Ex. A, Ex. 109, Zhou Tr., 194:8-13.)[10] Finally, the PTO selectively relies on and does not address the actual language in Braxton, which identifies ranges from 1:1, 2:1, 5:1, 10:1 up to 40:1 for the PEG moieties to the

[9] Dr. Zalipsky also opined that site-specific PEGylation, not lysine PEGylation, would have been a more favored approach for the claimed invention of the '171 Application. (Ex. A, Ex. 1, Corr. Zalipsky Rep.,¶ 62.) And the PTO's expert, Dr. Zhou admitted that Dr. Zalipsky "has already made a big contribution to the field" and that his "general opinion would be someone a skilled artisan will read and consider, reflect the general opinion in the field." (Ex. A, Ex. 109, Zhou Tr., 60:2-25.)

[10] Dr. Zalipsky never agreed that it would have been obvious to one of skill in the art to identify a workable PEGylation range for the previously claimed human-derived hyaluronidase. *See* PTO Br. at 19. Rather, Dr. Zalipsky clearly testified it's possible that one skilled in the art could attach many different PEG groups to a molecule, but the question is what the outcome would be in terms of properties of the final product. (Ex. A, Ex. 110, Zalipsky Tr. 222:13-223-7.) Notably, Dr. Zhou also agreed stating that you can PEGylate any protein but the outcome, such as denaturing of the protein killing its activity, varies from protein to protein. (Ex. A, Ex. 109, Zhou Tr., 91:5-92:12.)

protein. This conflicting evidence on what Braxton teaches, motivates and reasonably expects warrants denial. *See In re Dow Chemical Co.*, 837 F.2d 469, 473 (Fed. Cir. 1988) (In finding insufficient evidence to support a finding of obviousness, the Federal Circuit noted that "[i]n determining whether such a suggestion can fairly be gleaned from the prior art, the full field of the invention must be considered; for the person of ordinary skill is charged with knowledge of the entire body of technological literature, including that which might lead away from the claimed invention . . . It is indeed pertinent that these references teach against the present invention.")

Relying on the PTAB's summary decision, the PTO contends that Braxton and Thompson show that it is just routine optimization to achieve three to six PEG moieties on human-derived hyaluronidase. PTO Br. at 18. Dr. Flamion summarizes his pages of opinion directly to the contrary as follows:

> The problem is that the Board's conclusion on Braxton's teaching says nothing more than what was generalized in the art, namely attach one or more PEGs to a protein without abolishing its activity. *In my view, this is at best, a general plan or hypothesis and it does not teach one of skill the general or specific conditions required for any particular number of PEGs (much less where) to attach to the claimed composition which has approximately 447 amino acids* without abolishing it's *in vivo* activity, much less on a glycosylated protein where the glycans are essential for activity *in a manner that does not interfere with the in vivo activity at the distal tissues*. The claimed human-derived hyaluronidase has 30 lysines and an N-terminal amino group that result in a large number of potential PEGylation sites. Further: . . . (c) *neither Thompson nor Braxton provide the solution or the general or specific conditions applicable to this unique protein in order to achieve the invention claimed*; and (d) the published hyaluronidase assays that Dr. Zhou relies upon need to be modified in order to be used for the discovery of the new compositions claimed.

(Ex. A, Ex. 101, Flamion Rebuttal Rep., ¶ 11 (emphasis added).)

In sum, the PTAB never received this evidence on Braxton and Thompson, and that evidence, had the PTAB received it, shows the PTAB fundamentally erred in using Braxton and Thompson to provide the missing but required obvious analysis elements at least of (a) supplying

the missing range of PEG-moieties, (b) providing a motivation to combine the references, and (c) providing a reasonable expectation of success. *See In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, 676 F.3d 1063, 1069 (Fed. Cir. 2012) (a party seeking to invalidate a patent as obvious must demonstrate "that a skilled artisan would have reason to combine the teaching of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success from doing so.") At a minimum, factual disputes exist.

(c) The PTO's Legal Arguments on Genus/Species Case Law Is Unavailing

The PTO contends that it is appropriate for allegedly narrower claims to be declared obvious. This is not a case of obvious, narrower variations of already issued claims, as the PTO contends. But even if it is, it is "well-settled that a narrow species can be non-obvious and patent eligible despite a patent on its genus." *Abbvie*, 764 F.3d at 1379. Notably, *In re Schneller*, 397 F.2d 350 (CCPA 1968), as cited by the PTO, is limited to a particular fact situation (as the MPEP itself notes), further highlighting the need for underlying factual findings. *See Eli Lilly and Co. v. Genentech, Inc.*, No. 2:13-CV-07248, 2015 WL 12672089 at *6 (C.D. Cal., Mar. 5, 2015) ("Manual of Patent Examining Procedure observes that '[t]he decision in *In re Schneller* did not establish a rule of general application and thus is limited to the particular set of facts set forth in that decision.' MPEP ¶ 8.37.").

Bayer Pharma AG v. Watson Laboratories, Inc., 212 F. Supp.3d 489, 517 (D. Del. 2016) (citing *AbbVie*, 764 F.3d at 1379) is illustrative. In *Bayer*, the court found that both the reference patent and patent at-issue claimed the same combinations of two ingredients. *Id.* The court also noted differences between the claims, namely that the claims of the pending patent identified a precise recipe of specific dosages while the claim of the reference patent "far more broadly

claim[ed] an unspecified genus of multiple dosages." *Id.* The court ruled that the "differences between unspecified dosages in the [reference patent] and specified dosages in the [patent at-issue] [ ] are, in combination, patentably distinct differences" in finding the patent at-issue not invalid for obviousness. *Id.* at 519.

Similarly here, Claim 10 of the '429 Patent broadly claims an unspecified genus of human-derived hyaluronidase that is modified with any dextran or PEG molecule up to an undefined number. In contrast, the '171 Application Claim 264 requires a precise range of about three to six PEG moieties for the human-derived hyaluronidase pharmaceutical composition formulated for systemic administration.

Finally, the PTO's reliance on *Sun* to assert that the specification of the reference patent may be used in an obviousness-type double patenting analysis is also misplaced. Rather, and as a general rule, "the earlier patent's written description [is] considered only to the extent necessary to construe its claims." *Eli Lilly*, 689 F.3d at 1378-1379. The only other instance is "examination of the disclosed utility of the invention claimed in an earlier patent to address the question of obviousness." *AbbVie*, 764 F3d at 1381. *Sun* addresses this specific situation where "an earlier patent claims a compound, disclosing the utility of that compound in the specification, and a later patent claims a method of using that compound for a particular use described in the specification of the earlier patent." *Eli Lilly*, 689 F.3d 1368 at 1380 (citing *Sun Pharma. Ind. v. Eli Lilly & Co.*, 611 F.3d 1381, 1389 (Fed. Cir. 2010)). This is not the case in this action. As the court aptly noted in *Eli Lilly*, "Rather than a composition and a previously disclosed use, the claims at issue recite two separate and distinct chemical compounds." *Id.*

C. MATERIAL FACTS IN GENUINE DISPUTE EXIST WITH REGARD TO THE AGENCY'S OBVIOUSNESS TYPE DOUBLE PATENTING REJECTIONS OF THE PENDING CLAIMS BASED ON CLAIMS 4 AND 5 OF THE '431 PATENT IN VIEW OF BRAXTON AND THOMPSON

The PTO incorrectly argues that Claim 5 of the '431 Patent "is generally directed to a PEGylated hyaluronidase" like Claim 10 of the '429 Patent. PTO Br. at 26. This is patently incorrect: Claim 5 requires a pharmaceutical composition comprising a combination of human derived hyaluronidase ***and insulin***. The PTO's expert, Dr. Zhou, does not dispute this fact. (Ex. A, Ex. 111, Zhou Report, ¶ 129; Ex. 109, Zhou Tr., 207:20-23.) The PTO effectively asks this Court to ignore a material component of the claimed composition, namely insulin.

Dr. Zalipsky opined that one of ordinary skill in the art would not have used the teachings of Braxton and Thompson to make the claimed PEGylated human-derived hyaluronidase with about three to six PEG moieties for the same reasons discussed above. For example, Braxton and Thompson's preference for mono-PEGylation at the cysteine residues teach away from the about three to six PEG moieties as required in Pending Claim 264. (Ex. A, Ex. 86, Zalipsky Rebuttal Rep., ¶ 129.) Additionally, both Braxton and Thompson teach away from using the random, multi-PEGylation of lysine residues stating that such approach often leads to loss of activity and high composition heterogeneity making the conjugates unsuitable for pharmaceutical compositions. (*Id.*) Finally, that one of ordinary skill would not know whether 3-6 PEGs would retain sufficient activity and circulatory serum half-life to make it suitable for use as a pharmaceutical composition formulated for systemic administration as claimed in the '171 Application because the claimed human-derived hyaluronidase contains many residues that could potentially be PEGylated, and there are many additional variables that may lead to an uncertain outcome. (*Id.*)

There are also material disputes as to whether Claim 264's additional requirement that

the "pharmaceutical composition" is "formulated for systemic administration" renders it patentably distinct from Claim 5 of the '431 Patent. (*See supra* Section B.) Thus, Pending Claims 295-298, 300 and 303 are also patentably distinct from Claim 5 of the '431 Patent for the same reasons and further in view of the specifically claimed amino acid sequences. (*See supra*, fn. 7.)

The PTO's legal argument that the term "comprising" could also include additional therapeutic components, such as insulin is flawed as well. PTO Br. at 27-28. Although it is true that the word "'comprising'…creates a presumption that the body of the claim is open," *Crystal Semiconductor Corp. v. TriTech Microelecs. Int'l, Inc.*, 246 F.3d 1336, 1350 (Fed. Cir. 2001), it "is not a weasel word with which to abrogate claim limitations," *Dippin' Dots, Inc. v. Mosey*, 476 F.3d 1337, 1343 (Fed. Cir. 2007). "The presumption raised by the term 'comprising' does not reach into [a claim] to render every word and phrase therein open-ended…" *Id.* The claim must still be interpreted consistently with the specification. *Id.* at 1342-1343 (affirming the district court's limitation of the scope of a claim based on the patent's written description, despite the use of the word "comprising" in the claim). The '171 Application Pending Claims do not claim a pharmaceutical composition comprising a PEGylated human derived hyaluronidase with about three to six PEGs formulated for systemic administration *and* insulin. Thus, the use of the term "comprising" in Claim 264 does not broaden the scope of the claim to include additional therapeutic components as the PTO contends.

This important subject matter distinction renders the PTO's reliance on *Sun* to look to the '431 Patent's specification faulty. The PTO contends that the disclosure of an exemplary PEGylated hyaluronidase as described in Example 21 in the '431 Patent's specification should be used to determine whether the pending claims are obvious variants. This is improper however

because the '431 Patent's specification does not disclose the separate and distinct composition claimed in Claim 5 of the '431 Patent – a combination of human derived hyaluronidase *and* insulin. *See Eli Lilly*, 689 F.3d at 1380 (reference disclosure may be viewed only for claim construction or utility of a disclosed compound to assess whether subsequent pending claim to method of using that compound is described in the reference patent).

D. MATERIAL FACTS IN GENUINE DISPUTE EXIST WITH REGARD TO THE AGENCY'S OBVIOUSNESS TYPE DOUBLE PATENTING REJECTIONS BASED ON CLAIMS 5 AND 6 OF THE '081 PATENT IN VIEW OF BRAXTON AND THOMPSON

The PTO states that the single difference between claim 5 of the '431 Patent and claim 6 of the '081 Patent is the inclusion of a "cosmetic agent" instead of "insulin" and incorporates all of its reasons discussed regarding the '431 Patent to argue that Halozyme's pending claims are not patentably distinct from Claim 6 of the '081 Patent. The PTAB failed to consider the impact of this additional and required element of a "cosmetic agent" in its ODP analysis, including the factual disputes by experts. (Ex. A, Ex. 101, Flamion Rebuttal Rep. ¶¶ 89-92.) Thus, Halozyme also incorporates all of its reasons discussed above. *See supra* Sections B and C.

E. SECONDARY CONSIDERATIONS

The PTO also is not entitled to summary judgment on the existence of secondary considerations of nonobviousness of the '171 Application. Those secondary considerations are "'commercial success, long felt but unsolved needs, failure of others,' and unexpected results." *Novartis AG v. Noven Pharms. Inc.*, 853 F.3d 1289, 1292 (Fed. Cir. 2017) (quoting *Graham*, 383 U.S. at 17). As the nonmovant on this issue, Halozyme need only present evidence that—along with reasonable inferences – permits a reasonable jury to find in Halozyme's favor. As discussed below, the record satisfies Halozyme's burden of production, entitling it to a trial on the secondary considerations of nonobviousness.

1. Commercial Success

As an initial matter, a reasonable jury could find that the specific pharmaceutical composition product embodying the '171 Application (known as PEGPH20) has been commercially successful. The PTO contends that, because the product has not yet been approved by the FDA, commercial success is a legal impossibility. (ECF No. 89, PTO Br. at 29.) The PTO cites no authority for its proposition that only FDA-approved pharmaceuticals can exhibit commercial success, and Halozyme is aware of no such authority. Indeed, as a conceptual matter, the doctrine of commercial success is not limited to products that can be sold. If it was, the Federal Circuit would have rejected the applicant's claim of commercial success for its not-yet-approved pharmaceutical in *NantKwest, Inc. v. Lee* as a matter of law, but it did *not* do so, rejecting the claim because the applicant did not establish a nexus between the evidence of success and the claimed invention. 2015-2095, 2017 WL 1735330, at *8 (Fed. Cir. May 3, 2017). The question for the Court then is how to assess commercial success in the absence of sales.

The answer is to examine objective evidence of economic activity taken because of the features of PEGPH20 that Halozyme seeks to patent, and Halozyme has two forms of such evidence. *First*, Halozyme has raised significant sums of funds ($135 million) from investors because of PEGPH20. (Ex. B, LaBarre Decl. ¶ 2; Ex. B, Exs. 1-2.) Unlike in *NantKwest* (which also considered investment evidence, which makes the PTO's claim that "no case law" supports Halozyme curious), Halozyme has evidence connecting the investment to PEGPH20. The company's presolicitation filings with the SEC state that the purpose of the funds sought is to develop the PEGPH20 product. (Ex. B, Exs. 3-4.) In fact, the PEGPH20 product is the *only* specific purpose of the fundraising effort. The presentation made by Halozyme to potential investors is consistent. The first reason given by the company to invest in it – and the one to

which most of the presentation's space is devoted – is the PEGPH20. (Ex. B, Ex. 5 at 2, 3, 4–15, 20.) The reasonable inference from this evidence – which the Court is required to credit at this point – is that investors chose to invest in Halozyme because of the PEGPH20 product.

Second, other entities have entered clinical-study and other partnerships with Halozyme because of the PEGPH20 product. Halozyme has agreements with a nationally recognized cancer center, a public university, and a hospital system regarding clinical study of the PEGPH20 product and has been approached by at least two other universities. (Ex. B, LaBarre Decl. ¶ 4.) Most of these research partners sought Halozyme out and not the other way around. (Ex. B, Exs. 6-10.) In addition, Halozyme has an agreement with a large pharmaceutical company in which each company will study the other's product. (Ex. B, Ex. 11.) Finally, Halozyme has an agreement with a national organization focused on pancreatic cancer that will facilitate the clinical study of the PEGPH20 product. (Ex. B, Ex. 12.) Regardless of the status of them, or the fact that Halozyme derives no revenue from them, these arrangements demonstrate that others are seeking Halozyme out because of the PEGPH20 product. This evidence is sufficient for Halozyme to try the issue.[11]

2. Other Secondary Considerations

The PTO also asserts that Halozyme has not "established" unexpected results but that is not Halozyme's burden at this point, and Halozyme has sufficient evidence to support an unexpected-results argument to survive summary judgment. Indeed, Halozyme is prepared to provide substantial opinion evidence from Drs. Bruno Flamion and Samuel Zalipsky on this question. (*See, e.g.*, Ex. A, Ex. 1, Corr. Zalipsky Rep., ¶¶ 479-493; Ex. A, Ex. 86, Zalipsky

[11] If necessary, Jon Saxe – who has decades of experience in the pharmaceutical industry – will provide opinion evidence reinforcing Halozyme's position on this question. (Ex. A, Ex. 114, Saxe Rep. ¶¶ 1-41.)

Rebuttal Rep., ¶¶ 154-158; Ex. A, Ex. 47, Corr. Flamion Rep., ¶¶ 129-153; Ex. A, Ex. 101, Flamion Rebuttal Rep., ¶¶ 93-97; Ex. A, Ex. 27; Ex. A, Exs. 41, 80, 81, 82, 87, 92, 96, 97, 106.) The PTO quibbles with these experts' opinions (ECF No. 89, PTO Br. 29-30), but that strategy, at *best*, creates a material dispute of fact that necessitates trial. *See, e.g.*, *Joy Techs., Inv. v. Quigg*, 723 F. Supp. 227, 237-38 (D.D.C. 1990) (denying motion for summary judgment as to secondary considerations where some applicant provides evidence supporting its position).[12]

CONCLUSION

Accordingly, and for the reasons stated above, Halozyme urges the Court to deny the PTO's motion for summary judgment, grant Halozyme's motion for partial summary judgment, and set the case for trial.

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Respectfully submitted,

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[12] The PTO cites the testimony of Michael LaBarre for the proposition that a document submitted in prosecution of the '171 Application contradicted Halozyme's argument of unexpected results. ECF No. 89, PTO Br. at 29 (citing ECF No. 89, Ex. 9, LaBarre Dep. 133-34).) The cited testimony of Dr. LaBarre, however, is not admissible on this issue. Dr. LaBarre is not familiar with the document and therefore lacks foundation to testify about it. (Ex. A, Ex. 123, LaBarre Tr. at 130.) All Dr. LaBarre can do – which is what the PTO asked him to do at his deposition – is to read the document and speculate as to its content. (*Id.* at 130–34.) But Dr. LaBarre has not been disclosed as an expert in this case and will testify as a fact witness, and his lack of personal knowledge about the document makes the topic inapt for lay-opinion testimony under Federal Rule of Evidence 701.

CERTIFICATE OF SERVICE

I hereby certify that on September 8, 2017, I electronically filed the foregoing **Halozyme's Brief in Support of Its Motion for Partial Summary Judgment and in Opposition to the PTO's Motion for Summary Judgment** with the Clerk of Court using the ECF system, which will send notification of such filing to all ECF participants.

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